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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,396	12/28/2001	Ryoichi Nagata	2001_1906A	8735

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WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/12/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,396	NAGATA, RYOICHI	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under Rule 1.114 filed 09/09/03 is acknowledged.

Claims 1, 2, 5, 7 and 9-12 are pending. Claims 3, 4, 6 and 8 have been cancelled. Claims 1, 2, 5, 7 and 9-12 are rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagawa (US Pat. No. 6,197,328 B1) *or* Yanagawa (EPO 0 681 833 A2).

Yanagawa *(US '328)* teaches a nasally administrable composition, comprising an effective amount of a physiologically active compound, insulin and a fine particulate carrier, calcium carbonate having many pores, whereby the porous calcium carbonate has a mean particle size from 15-300 microns and a particle surface area from 0.1 m^2/g to 0.4 m^2/g and wherein the nasally administered formulation contains insulin dispersed and homogeneously adsorbed onto the calcium carbonate carrier and is highly absorbable into the body via the nasal route (see reference column 1, line 1 – column 8, line 16); examples and abstract.

According to Yanagawa, the nasally administrable composition can nasally administer the physiologically active compound, insulin, with higher bioavailability and with less irritability than preparations so far proposed using the carrier, wherein the carrier adheres to the mucous membrane of the nasal cavity (col. 1, lines 45-51).

Yanagawa teaches that the carrier of his invention is characterized by homogeneous dispersion to the interior of the nasal cavity, adhesion to the mucous membrane of the nasal cavity without inhalation to the lung, and the sustainable adhesion of the carrier on the mucous membrane by its own weight and particle size. Such a carrier is a calcium compound, such as *calcium carbonate,* calcium stearate, calcium chloride or calcium hydroxide, wherein among them, calcium carbonate is

preferred and has a mean particle size from 15-300 microns and a particle surface area from 0.1 m^2/g to 0.4 m^2/g. The carrier to be used has many pores on the surface as a result of granulation or re-granulation with carriers with each other (col. 2, line 54 – col. 3, line 10).

Examples of physiologically active compounds include peptides, antidiabetics/symptomatic antidiabetics, etc., wherein peptides, such as insulin are preferred. A preferable mode of the invention is a nasally administrable composition having fine particulate of insulin dispersed and adsorbed homogeneously onto the unique mixed carrier of calcium carbonate and high substituted hydroxypropylcellulose (HPC –H) (col. 3, lines 27-55).

The physiologically active compound, insulin, is contained at a rate from 0.0001% to 30% by total weight of the composition (col. 3, line 56 – col. 4, line 4). This range meets the applicant's claimed range of an insulin content of 0.1-50% by weight.

The composition may further contain conventional excipients such as fillers, stabilizers, binders, lubricants and the like (col. 4, lines 11-20).

The examples demonstrate various preparations of the composition of the invention. Test Example 2 at column 5, demonstrates the teaching of a preparation comprising insulin as the selected physiologically active compound, calcium carbonate as the selected carrier and HPC – H was selected as the absorption accelerator to prepare the composition. These ingredients were admixed to make the composition containing insulin 50 IU/50 mg of calcium carbonate/5mg of HPC – H capsule and the resulting mixture was filled into capsules. The mean particle size of each carrier was

from 20 microns to 45 microns. The resultant composition was nasally administered once at a dose of 50 mg. The composition containing 50 IU of insulin attained a high degree of absorption of insulin into the blood through the nasal route compared with the comparative composition in which 100 IU of insulin was contained.

Similarly at column 6, a powdery insulin composition for nasal administration was prepared using ingredients of insulin, calcium carbonate and HPC – H.

With regards to the applicants claimed ranges, the prior art teaches similar or overlapping ranges that read on the ranges as instantly claimed. For instance, Yanagawa teaches a mean particle size of the porous calcium carbonate to be 15 – 300 microns (applicant's range is 20 – 32 microns). Additionally, the insulin content taught by the prior art is from 0.0001% to 30% (applicant's range is 0.1-50%). The particle surface area of calcium carbonate taught by Yanagawa is from 0.1 m^2/g to 0.4 m^2/g (applicant's range is 1.5 m^2/g or greater). The surface area taught is slightly less than applicant's claimed surface area, however, it would have been obvious to one of ordinary skill in this art that suitable ranges or amounts could be determined through routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters.

Regarding the particular shape of the crystals (i.e., trabeculate, needle-shaped or aggregation of parallel intergrowth), one of ordinary skill in this art would determine suitable variations of form, which meet the intended or desired purpose.

There is no significant distinction observed between the instant invention and the prior art, since the prior art clearly teaches a nasally administered formulation of insulin,

comprising porous calcium carbonate as its carrier, wherein the calcium carbonate has similar particle size and surface area as claimed and whereby the insulin is dispersed and adsorbed homogeneously onto the calcium carbonate. Hence, the instant invention is rendered unpatentable and obvious over Yanagawa (US '328).

Yanagawa ***(EPO '833 A2)*** teaches a nasally administrable composition containing a physiologically active substance – insulin, homogeneously dispersed in and adsorbed homogeneously onto a unique crystalline metal compound carrier, calcium carbonate, whereby the carrier has a mean particle size of not more than 250 microns, or more preferably 30 microns to 60 microns and whereby the formulation is administered via the nasal cavity in a powder formulation (see reference pages 2-4) and Abstract.

According to Yanagawa, the composition, which is prepared by homogeneously dispersing the physiologically active peptide, insulin, in a unique carrier, can be applied to the mucous membrane of the nasal cavity to thereby allow a clinically effective treatment. Yanagawa teaches that the technique of homogeneously dispersing a physiologically active peptide, insulin, in a carrier, calcium carbonate, provides an equal or higher bioavailability compared with that obtained by injection or oral administration (page 3, lines 2-5).

The carrier includes a calcium compound, such as calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, etc., wherein calcium carbonate is particularly preferred (page 3, lines 33-53).

Various physiologically active substances may be used, and include antidiabetics/symptomatic antidiabetics. A preferred mode of the invention is a nasally administrable composition comprising a physiologically active substance and a physiologically acceptable powdery or crystalline polyvalence metal carrier whose mean particle size is not more than 250 microns and more preferably 30-60 microns (page 4, lines 20-42). Among the physiologically active peptides, peptide hormones, such as insulin are preferred (pg. 5, lines 37-42).

The physiologically active peptide is contained in the composition at a rate from approximately 0.005% to approximately 30% (pg. 6, lines 28-31). This range meets the applicant's claimed range of 0.1-50% insulin content.

The examples taught by Yanagawa show the use of glucagon in combination with calcium carbonate and the use of insulin with hydroxyapatite. Both examples teach the use of peptide hormones in combination with an accepted carrier (see pages 7, 19 and 25).

Regarding the particular shape of the crystals (i.e., trabeculate, needle-shaped or aggregation of parallel intergrowth), one of ordinary skill in this art would determine suitable variations of form, which meet the intended or desired purpose. Furthermore, the prior art teaches a crystalline or powdery carrier.

Regarding the instant ranges of particle diameter and surface area for calcium carbonate, Yanagawa teaches similar or overlapping ranges for the particle size and is silent as to the specified surface area. However, it is deemed obvious to one of ordinary skill in this art that suitable ranges or amounts could be determined through routine or manipulative experimentation to obtain the best possible results, as these are considered variable parameters. No criticality is seen in the instant ranges, since the prior art clearly teaches a nasally administered formulation comprising similar ingredients (i.e., insulin, calcium carbonate) for a similarly intended purpose as the applicants and in the same field of endeavor, whereby high bioavailability of insulin is obtained using nasal administration. Hence, the instant invention is rendered obvious and unpatentable over Yanagawa (EPO '833 A2).

Response to Arguments

Applicant's arguments filed 09/09/03 have been fully considered but they are not persuasive. The applicant argued, "Yanagawa (EPO '833) discloses calcium carbonate only as an example of physiologically acceptable powdery or crystalline polyvalence metal compound carriers and makes no mention of the properties of the calcium carbonate".

This argument has been fully considered, but was not found to be persuasive. Yanagawa teaches a nasally administered formulation of insulin, comprising various

carriers wherein calcium carbonate is particularly preferred. Yanagawa teaches that the mean particle size of the calcium carbonate is most preferably 30-60 microns. The applicants argument that the properties of calcium carbonate are not mentioned, since Yanagawa teaches a formulation comprising similar ingredients for a similar intended purpose as the applicants and therefore the properties imparted by those ingredients would also be similar. Furthermore, it is of no moment that the prior art recognize each and every property that accrues from each ingredient, merely that the prior art recognize the teaching of that particular ingredient for a similar purpose is sufficient.

The applicant also argued, "Neither Yanagawa nor Staniforth et al. mention or suggest porous particles of calcium carbonate, which is used in the present invention."

This argument has been fully considered, but was not found to be persuasive. The applicants recite 'porous' calcium carbonate. However, the examiner notes that calcium carbonate is a material, that in itself is considered to have many pores on its surface or be porous and as such the inclusion of 'porous' calcium carbonate is inherent to the formulation of Yanagawa.

With regards to the applicant's arguments regarding Staniforth et al. (US '438), these arguments have been considered but are rendered moot in view of the new grounds of rejection.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (703) 308-4429. The examiner can normally be reached on Monday through Friday from 7:00A.M. to 4:30P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns
November 04, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600